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10/068,238	02/05/2002	Constance A. Bell	07039-372001	7696

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 01/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,238	BELL ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on November 9, 2005 has been entered.

2. Applicants' arguments did not overcome any of the previously presented rejections. The arguments are addressed in the "Response to Arguments" section below.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on November 9, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Applicant's arguments filed July 21, 2005 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 57, 59, 61, 63, and 69 under 35 U.S.C. 103(a) over Ramisse et al., Makino et al. and Buck et al., Applicants argue the following:

a) Buck et al. teaches an automated sequencing reaction which is significantly different than a PCR amplification reaction, which uses at least two oligonucleotides, or a real-time PCR, in which four oligonucleotides are used, therefore primer design for real-time amplification is not always predictable. In support of this argument Applicants submitted the references of Elnifro et al.,

Tichopad et al., Abd-Elsalam, all of which deal with primer design in general, a reference of Csordas et al., which deals with selection of primers for detection of Salmonella enterica by real-time PCR and a reference of Ballard et al., which describes primer sets for identification of vanB gene in enterococci.

b) The primer and probe sequences of SEQ ID NO: 1-4 are not obvious because their combination leads to high sensitivity and specificity towards their targets, as shown in Examples 1-4. Applicants further argue that each of the probes (SEQ ID NO: 3 and 4) has a particular melting temperature which can be used to confirm the presence of B. anthracis in the sample.

c) In re Deuel is not relevant to the instant claims since the case dealt with the obviousness of nucleic acid sequences over references which disclosed an amino acid sequence, therefore In re Deuel does not indicate that a primer or probe sequence complementary to the target is a structural homolog.

d) Claimed primers and probes are not obvious over the cited references as supported by In re Bell.

e) A longer sequence can be viewed as representing a very large genus of possible sub-sequences from which the primers and probes can be selected. Applicants cite in Re Jones in support of this view.

Regarding a), sequencing, PCR amplification and real-time PCR are the same process which may differ in the number of primers involved. All three processes require the same fundamental steps: design and synthesis of primers, annealing of primers to a selected sequence and extension of the 3' ends of the primers by a polymerase. Applicants argue that sequencing uses only one primer, however, this is not true, since usually both DNA strands are sequenced to avoid errors. Further, for very long sequences of more than 1000 bp, more than one sequencing primer is used. Therefore,

both sequencing and PCR require at least two primers, one for each strand of the DNA. Further, even though real-time PCR may require three or four oligonucleotides (one or two of them serving as a probe), only two of them are primers, while the other serve as probes binding to the amplified fragments. Therefore, sequencing, PCR amplification and real-time PCR use two primers in a process governed by the same principles. In conclusion, selection of primers for sequencing is not qualitatively different from the selection of primers for PCR amplification or real-time PCR. Finally, Buck et al. provides evidence that 95 18 bp primers selected from a sequence of 300 bp at 3 bp intervals all perform as specific primers, and thus Buck et al. provides EVIDENCE of the equivalence of primers in extension type assays, which include PCR. Applicants' arguments cannot rebut this evidentiary showing.

The references provided by Applicants do not provide evidence that Applicants' primer selection was in any way unique. The references of Elnifro et al., Tichopad et al., Abd-Elsalam, all of which deal with primer design in general, and contain information well known to one of skill in the art how to select primers. The reference of Csordas et al., which deals with selection of primers for detection of Salmonella enterica by real-time PCR and a reference of Ballard et al., which describes primer sets for identification of vanB gene in enterococci, are not pertinent to Applicants' case, since they deal with the selection of primers for very different sequences. Applicants' own evidence in form of Example 1, first paragraph, shows that the only step undertaken in primer and probe design was analysis of sequences using primer design OLIGO software from Molecular Biology Insights, Inc. (Cascade, OR). There is no evidence in Applicants' disclosure that any of the primers selected were additionally tested before being used in the amplification reactions. As Ramisse et al. teach selection of their primers from the same gene sequences using primer design software Oligo from MedProbes (Oslo, Norway), their primers would most likely function in real-

time PCR as well. Finally, the limitation that the primers be used for real-time PCR is not present in the claims, and even if it were, it would still require evidence that these primers were specifically selected for this purpose and that other primers selected from the same gene sequences would not function under conditions of real-time PCR.

Regarding b), Applicants state in Examples 4 and 5 that of 32 B. anthracis isolates 28 were positive for all three target genes, and one was false negative for capB, and that the primers and probes selected by Applicants had no cross-reactivity with other bacterial species. However, primers and probes of Ramisse et al. exhibited the same properties (Table 1). All of the B. anthracis strains possessing the pXO1 plasmid were detected with the lef and pag primers, and all of the B. anthracis strains possessing the pXO2 plasmid were detected with the cap primers, and all of the pXO1/pXO2 strains were detected with all three primers. In addition, the cap, lef and pag primers did not exhibit cross reactivity with other Baccilus species or other bacterial species. Therefore, primers of Ramise et al. selected from other parts of the same genes as primers selected by Applicants possess the same properties of sensitivity and specificity. Finally, the particular melting temperatures of the probes are not limitations in the claims, and every primer or probe has a melting temperature which is dependent on the solution composition and the primer or probe sequence, therefore a melting temperature is an inherent property of any primer or probe.

Regarding c), it is not relevant what In re Deuel was about, since the Court's statement provided in the rejection refers to any structurally similar compounds. The fact that In re Duel does not specifically discuss primers or probes and target nucleic acids does not diminish the relevance of that statement. In fact, one would be hard pressed to find better examples of structural homologs than primers and probes, which are parts of the same target nucleic acid molecule by virtue of being complementary to one of the strands of the molecule.

Regarding d), the case of In re Bell the issue was whether the presence of an amino acid sequence of a protein in prior art combined with knowledge of how to isolate genes would render the claimed nucleic acids obvious. Therefore, since translating an amino acid sequence into a nucleic acid results in many possible nucleic acids because of the codon degeneracy, the Court concluded that the nucleic acids would not have been obvious. However, the issue in the instant case is whether two different fragments selected from the same nucleic acid sequence would be equivalent in their function as primers, therefore In re Bell is irrelevant to the instant claims.

Regarding e), the genus of nucleic acids represented by fragments of a given nucleic acid sequence is not very large. For example, the capB gene is about 1490 bp long. The number of 20 bp oligonucleotides derived from that sequence every base pair would be 1490-20 +1 =1471 oligonucleotides, which is not a huge genus. Of course using a primer design software would allow elimination of structurally unwanted primers, making the number even smaller. Applicants cite In re Jones as supporting the notion that the genus does not make the species obvious. However, In re Jones dealt with an issue of whether "Claimed novel salt of acid commonly known as "dicamba" is not so closely related in structure to substituted ammonium salts disclosed in prior patent as to be prima facie obvious, since claimed salt is primary amine with ether linkage, whereas diethanolamino salt disclosed in reference patent is secondary amine without ether linkage, since claimed salt is plainly acyclic or linear, whereas morpholino salt, which is only substituted ammonium salt of dicamba with ether linkage disclosed in reference patent, is cyclic in structure, and since isopropylamino salt disclosed in reference patent is primary amine, but has iso-structure quite different from that of claimed salt." (first paragraph). Therefore, the case dealt with chemical compounds with different chemical structures. In the instant case the genus is a nucleic acid molecule of the same structure as the primers and probes derived from it, since they form parts of

the complementary strands of the nucleic acid. Thus, the holdings of In re Jones do not apply to the instant case.

The rejections are maintained.

B) Regarding the rejection of claims 58, 60, 62 and 64 under 35 U.S.C. 103(a) over Ramisse et al., Makino et al. and Buck et al., Applicants reiterate the argument that the references do not teach or suggest the particular primers or probes and arguments about Buck et al. and reasoning based on In re Deuel. These arguments were addressed above.

The rejections are maintained.

C) Regarding the rejection of claims 67 and 68 under 35 U.S.C. 103(a) over Ramisse et al., Makino et al. and Buck et al., Applicants argue that these claims are not obvious over the cited references. As these two claims are drawn to instructions for using primers and probes, they do not contain limitations which limit the structure of the primers and probes, and therefore are irrelevant from the point of view of comparing the primers and probes with prior art.

The rejections are maintained.

D) Regarding the rejection of claims 65 and 66 under 35 U.S.C. 103(a) over Ramisse et al., Makino et al. and Buck et al., further in view of Wittwer et al. and Qi et al., Applicants reiterate the arguments regarding the references, specificity and selectivity of the claimed sequences, probes' melting temperatures and In re Deuel.

These arguments were addressed above.

The rejections are maintained.

E) Regarding the rejection of claims 70, 72, 74, 76 and 82 under 35 U.S.C. 103(a) over Ramisse et al., Price et al. and Buck et al., Applicants reiterate the arguments regarding specificity and selectivity of the claimed sequences, Buck et al. and reasoning based on In re Deuel.

These arguments were addressed above.

The rejections are maintained.

F) Regarding the rejection of claims 71, 73, 75 and 77 under 35 U.S.C. 103(a) over Ramisse et al., Price et al. and Buck et al., Applicants reiterate the arguments regarding specificity and selectivity of the claimed sequences, Buck et al. and reasoning based on In re Deuel.

These arguments were addressed above.

The rejections are maintained.

G) Regarding the rejection of claims 80 and 81 under 35 U.S.C. 103(a) over Ramisse et al., Price et al. and Buck et al., Applicants argue that these claims are not obvious over the cited references. As these two claims are drawn to instructions for using primers and probes, they do not contain limitations which limit the structure of the primers and probes, and therefore are irrelevant from the point of view of comparing the primers and probes with prior art.

The rejections are maintained.

H) Regarding the rejection of claims 78 and 79 under 35 U.S.C. 103(a) over Ramisse et al., Price et al. and Buck et al., further in view of Wittwer et al. and Qi et al., Applicants reiterate the arguments regarding the references, specificity and selectivity of the claimed sequences, probes' melting temperatures and In re Deuel.

These arguments were addressed above.

The rejections are maintained.

I) Regarding the rejection of claims 83, 85, 87, 89 and 95 under 35 U.S.C. 103(a) over Ramisse et al., Bragg et al. and Buck et al., Applicants reiterate the arguments regarding the references, specificity and selectivity of the claimed sequences, Buck et al. and reasoning based on In re Deuel.

These arguments were addressed above.

The rejections are maintained.

J) Regarding the rejection of claims 84, 86, 88 and 90 under 35 U.S.C. 103(a) over Ramisse et al., Bragg et al. and Buck et al., Applicants reiterate the arguments regarding Buck et al. and reasoning based on In re Deuel.

These arguments were addressed above.

The rejections are maintained.

K) Regarding the rejection of claims 93 and 94 under 35 U.S.C. 103(a) over Ramisse et al., Bragg et al. and Buck et al., Applicants argue that these claims are not obvious over the cited references. As these two claims are drawn to instructions for using primers and probes, they do not contain limitations which limit the structure of the primers and probes, and therefore are irrelevant from the point of view of comparing the primers and probes with prior art.

The rejections are maintained.

L) Regarding the rejection of claims 91 and 92 under 35 U.S.C. 103(a) over Ramisse et al., Bragg et al. and Buck et al., further in view of Wittwer et al. and Qi et al., Applicants reiterate the arguments regarding the references, specificity and selectivity of the claimed sequences, probes' melting temperatures and In re Deuel.

These arguments were addressed above.

The rejections are maintained.

M) Regarding the rejection of claim 96 under 35 U.S.C. 103(a) over Ramisse et al., Makino et al., Price et al., Bragg et al. and Buck et al., Applicants reiterate the arguments regarding Buck et al., specificity and selectivity of the claimed sequences and reasoning based on In re Deuel.

These arguments were addressed above.

The rejections are maintained:

Claim interpretation

5. In claims 67, 68, 80, 81, 93 and 94, the limitation of a package insert having instructions for using primers and probes is not taken into account when comparing claims with the prior art, since the instructions (printed matter) do not constitute a structural limitation on primers or probes.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 57-64 and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS and in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) Regarding claims 57-64 and 67-69, Ramisse et al. teach primers for detection of capB gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-4.

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Makino et al., since Ramisse et al. expressly teach primer selection for B. anthracis detection using commercially available software from the B. anthracis published sequences and since Makino et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of

ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

9. Claims 65 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office

action) as applied to claims 61 and 63 above, and further in view of Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 65 and 66, Ramisse et al. teach primers for detection of capB gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 65 and 66, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 65 and 66, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature

cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. ... The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

10. Claims 70-77 and 80-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action).

A) Regarding claims 70-77 and 80-82, Ramisse et al. teach primers for detection of pagA gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 5-8.

B) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the pagA gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the pagA gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the pagA gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the pagA gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the pagA gene (Table 2). Further, Price et al. teach primers for amplification of pagA gene (Table 1), which were designed from published pag sequence (page 2358, sixth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Price et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Price et al. provide such published sequences for the software program to analyze, and also teach primers for amplification of pagA.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate

compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

11. Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action), as applied to claims 74 and 76 above, and further in view of Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 78 and 79, Ramisse et al. teach primers for detection of pagA gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 78 and 79, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 78 and 79, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and

4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. ... The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

12. Claims 83-90 and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) Regarding claims 83-90 and 93-95, Ramisse et al. teach primers for detection of lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 9-12.

B) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the lef gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the lef

gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the lef gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the lef gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the lef gene (Table 2). Further, Bragg et al. teach primers for sequencing of lef gene, which span the entire sequence of the gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Bragg et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Bragg et al. provide such published sequences for the software program to analyze. Further, Bragg et al. teach primers spanning the entire sequence of the lef gene.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate

compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

13. Claims 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), as applied to claims 87 and 89 above, and further in view of Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997 ; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 91 and 92, Ramisse et al. teach primers for detection of lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 91 and 92, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 91 and 92, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and

4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. ... The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

14. Claim 96 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS; cited in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action).

A) Regarding claim 96, Ramisse et al. teach primers for detection of capB gene, pag A gene and lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-12.

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

C) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the pagA gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the pagA gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the pagA gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the pagA gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the pagA gene (Table 2). Further, Price et al. teach primers for amplification of pagA gene (Table 1), which were designed from published pagA sequence (page 2358, sixth paragraph).

D) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the lef gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the lef gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the lef gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the lef gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the lef gene (Table 2). Further, Bragg et al. teach primers for sequencing of lef gene spanning the entire length of the gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequences of Makino et al., Price et al. and Bragg et al., since Ramisse et

al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Makino et al., Price et al. and Bragg et al. provide such published sequences for the software program to analyze.

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> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

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sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

15. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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PATENT EXAMINER
Teresa Strzelecka
1/20/06